REMARKS

Claims 1-8 are pending. Claims 2-3 have been amended.

Claim Rejections Under 35 USC § 112

The Examiner has rejected claims 2-3 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. According to the Examiner, claims 2-3 are indefinite, because the phrase "...or a dose of another opioid which is a morphine equivalent dose of between 30 and 100 oral mg/day of methadone" is tantamount to the phrase "for example" and is not limiting. Applicants respectfully traverse.

The phrase in question defines the patients to be treated as ones receiving any opioid in a morphine equivalent dose of 30 to 100 mg/day of methadone. A morphine equivalent dose has been used by those of ordinary skill in the art as a standard against which the dose of other opioids can be titrated. See, for example, US Patent 5,317,022. Morphine equivalent doses for many other opioids were well known by those of ordinary skill in the art, several being exemplified in the present application. The term "morphine equivalent dose" also is defined on page 6, second paragraph, of the instant application: "[b]y morphine equivalent dosage is meant representative doses of other opioids which equal 1 milligram of morphine, for example, 10 mg of meperidine, 1 mg of methadone, and 80 μg of fentanyl." One of ordinary skill in the art would understand the metes and the bounds of what is claimed when the claim is read in the light of the specification. Therefore, the claim meets the requirements of 35 U.S.C. §112, second paragraph. It respectfully is requested that this rejection be withdrawn.

Claim Rejections Under 35 USC § 102

The Examiner has rejected claims 1-7 under 35 USC §102(b) as being anticipated by US Patent No. 4,176,186 to Goldberg et al. The Examiner states that Goldberg et al. teach a method for treating the intestinal motility inhibiting side-effects of, for example, methadone with quaternary derivatives of noroxymorphone (QDNM) by a coated pill, tablet, solution, suspension, etc. wherein the dosage unit is from 0.133 mg/kg to 1.33 mg/kg. The Examiner additionally states that, although Goldberg et al. do not specifically teach the plasma

concentrations reached of the actives, such is necessarily the case since the dosage of equivalent administration is the same. In addition, the Examiner states that products of identical chemical composition can not have mutually exclusive properties and, therefore, alleges that if the prior art teaches the identical chemical compound, the properties that Applicants disclose and/or claim are necessarily present. Applicants understand the Examiner to mean that the limitations of these claims are inherent in Goldberg et al. Applicants respectfully traverse.

The instant claims are directed to subject matter that is not inherent in Goldberg et al. The instant claims are directed to methods of treating chronic opioid patients. Applicants discovered that patients taking opioids chronically are surprisingly sensitive to quaternary derivatives of noroxymorphone. As discussed at page 5 and in the examples of the instant application, laxation was induced in chronic opioid users whereas no laxation was induced in acute opioid users. Goldberg et al., on the other hand, do not mention chronic opioid users. Treating this patient population is not inherent in Goldberg et al.

The instant claims also are directed to achieving laxation in a chronic opioid user. Laxation is a highly complex, coordinated physical movement resulting in the discharge of fecal waste. The cited Yuan et al. reference (Clin. Pharmacol. Ther. 1996; 59; 469-75) shows that I.V. treatment with methylnaltrexone does not induce laxation in acute opioid users. Goldberg et al. does not contradict the Yuan et al. teaching. This is in contrast to the result demonstrated and claimed in the instant application respecting the treatment of chronic opioid users. Applicants urge that an aspect of the present invention is the discovery that chronic opioid users have increased sensitivity to MNTX. As a result, in the present invention, laxation was achieved when treating chronic opioid users with relatively low doses of methynaltrexone. This is not inherent in the teaching by Goldberg et al. as evidenced by Yuan et al.

The Examiner appears to incorrectly equate increasing intestinal motility with laxation. The prior art Yuan et al. reference shows that I.V. treatment with methylnaltrexone, even at the maximum safe tolerated dose, will favorably affect intestinal motility, but will not induce laxation in acute opioid users. This is consistent with Goldberg et al., which teach favorably affecting intestinal motility in acute opioid users. There is no mention whatsoever of chronic opioid users or laxation in Goldberg et al.

The instant invention further is directed towards achieving laxation with oral administration of quaternary derivatives of noroxymorphone at a dose between 0.3 and 3.0 mg/kg, wherein the plasma levels do not exceed 100 ng/ml. This aspect of the invention is not inherent in Goldberg et al. Whether an oral dose would result in plasma levels below 100 ng/ml depends on many factors, including the concentration of the drug, and the formulation of the drug. Controlling formulation parameters to keep plasma levels below 100 ng/ml is not inherent in or suggested by Goldberg. Treating chronic opioid users and achieving laxation while maintaining plasma levels below 100 ng/ml is not inherent in (or remotely suggested by) Goldberg et al. As shown in Example 3 of the instant specification, laxation was induced in chronic opioid patients treated with oral doses of MNTX between 0.3 and 3.0 mg/kg while the peak plasma levels of MNTX remained well below 100ng/ml (Example 3, page 21, the peak plasma levels for the subjects ranged from undetectable to 26 ng/ml.)

In summary, the instant claims are directed to (i) "inducing laxation" in (ii) "chronic opioid patients" using (iii) oral dosing in amounts that yield "less than 100 ng/ml peak plasma levels" of antagonist. These aspects of the claims are not anticipated by Goldberg et al. It respectfully is requested that the rejection on this basis be withdrawn.

Claim Rejections Under 35 USC § 103

The Examiner has rejected claims 1-8 under 35 U.S.C. 103(a) as being unpatentable over Yuan et al. Clin. Pharmacol Ther. 1996;59:469-75 in view of US Patent No. 4,176,186 to Goldberg et al. Applicants respectfully traverse.

Yuan et al. report a trial wherein healthy opioid naïve volunteers received a single acute dose of opioid and 0.45 mg/kg methylnaltrexone I.V. The methylnaltrexone inhibited opioid-induced delay in oral-cecal transit time without affecting analgesia. In contrast to the claimed invention, the subjects in Yuan et al. were not chronic opioid users, did not laxate, and did not receive doses that would keep peak plasma levels below 100 ng/ml.

The instant claims, on the other hand, are directed to (i) "inducing laxation" in (ii) "chronic opioid patients" using (iii) oral dosing in amounts that yield "less than 100 ng/ml peak plasma levels" of antagonist. These aspects of the claims are not obvious in view of Yuan et al.

If anything, Yuan et al. teach away from the invention in that Yuan et al. teach that IV doses which would have resulted in peak plasma levels above 500 ng/ml did not induce laxation. It would not have been expected, based on Yuan et al., that a chronic opioid user would require lower doses, resulting in plasma levels of 100 ng/ml or less, would induce laxation. It respectfully is requested that the reject on this basis be withdrawn.

The Examiner considers Yuan et al., Effects of Methylnaltrexone on Chronic Opioid-Induced Gut Motility and Transit Time Changes, Abstracts from the Eighth International Symposium on Pain, Anesthesia and Endocrinology. September 18-19, 1997 equivalent to US Patent No. 4,176,186 to Goldberg et al. Although the Applicants do not agree with the Examiner's characterization, the Examiner's attention is directed to the above arguments made in response to the rejections over Goldberg et al. In addition, this reference does not disclose inherently or otherwise a dosing regimen resulting in peak plasma levels below 100 ng/ml.

Double Patenting Rejections

The Examiner has provisionally rejected claims 1-8 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over various claims of co-pending Application Nos. 10/778,268, 10/779,128, 10/785,668, 10/278,630, and 10/779,129 in view of US Patent No. 4,176,186 to Goldberg et al. and Yuan et al., Clin. Pharmacol Ther. 1996;59:469-75. Applicants understand that in accordance with Section 804 of the MPEP, a "provisional" double patenting rejection will continue to be made by the Examiner until the "provisional" double patenting rejection is the only rejection remaining in one of the applications. Accordingly, Applicants will address the appropriateness of these "provisional" double patenting rejections after the Examiner withdraws all other reasons for rejection.

The Examiner rejected claims 1-8 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-38 of U.S. Patent No. 6,608,075 in view of Yuan et al., Clin. Pharmacol Ther. 1996;59:469-75. Applicants respectfully traverse. The '075 patent claims are not directed to the subject matter of the instant claims, that is, treating chronic opioid patients and inducing laxation. It respectfully is requested that the obviousness-type double patenting rejections on these bases be withdrawn.

The Examiner rejected claims 1-8, under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-36 of U.S. Patent No. 6,559,158 in view of US Patent No. 4,176,186 to Goldberg et al. Without conceding the correctness of this rejection, in order to advance prosecution, Applicants herewith submit the appropriate terminal disclaimer in compliance with 37 CFR §1.321(c).

Summary

Claims 1-8 are pending. Claims 2-3 have been amended.

In view of the above amendment, Applicants believe the pending application is in condition for allowance.

Respectfully submitted,

By _____

Edward R. Gates
Registration No.: 31,616
WOLF, GREENFIELD & SACKS, P.C.
Federal Reserve Plaza
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
(617) 646-8000

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